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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,098	06/20/2001	Robert Stuart Coffin	117-340	7947

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,098	COFFIN ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *13-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) ✓
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5&9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary amendment of paper No. 6 filed on August 15, 2001 has been noted. Claim 13 is canceled. Claims 1-12 and 14-27 are pending.

Petition

The petition under Rule 181 filed on paper No. 12, August, 16 2002 has been received by the office. The application will be sent back to the special program of the Technical Center for decision on petition after the office action is mailed out.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-12 and 27 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the prior art cited does not teach the common technical feature of the invention.

2. Applicants' argument has been respectfully considered; however, it is not found persuasive. In the instant case, the claimed invention is drawn to a method for propagating a mutated HSV virus with mutation in VP16 gene or the mutant plus ICP4 gene mutation, wherein the VP16 is supplied in trans with a cell line express a functional herpes simplex virus (HSV) VP16 polypeptide or homologue thereof. The VP16 is capable of complementing the defective VP16 function but not undergo homologous recombination with the VP16 gene in the virus. This technical feature is already taught in the art as evidenced by Wienhermer et al. and Latchman et al. as described in the previous office action. For example, Wienhermer et al. teach to use a cell line to grow the mutated HSV-1 virus with VP16 mutation, in1814, wherein the cell line is transfected to express the VP16 of HSV-2, which is the homology of the VP16 of HSV-1.

3. Applicants further argue that Weinhermer et al. does not teach that is may be desirable to exclude the possibility of homology recombination occurring between an endogenous viral gene and the gene supplied in trans. Applicants also argue that neither Winheimer et al. nor Lachmenn et al teach or suggest that a VP16 gene homologue having a suitable low sequence identity to prevent homologues recombination occurring with the endogenous gene (i.e. as little as 50%) will be capable of complementing the function of the endogenous gene.

4. Applicants' argument has fully considered; however, it is not found persuasive because the limitation of the low sequence identity does not appear in any of the claims, and neither Winheimer et al. nor Lachmenn et al. teach that the homologue of VP16 of HSV-1 that they have been used have undergone the homology recombinant. For example, Winheimer et al. only teach that the 22-3 mutation alters the activity of a VP16 homology of HSV-2 and the 16-8 cells express functional VP16 capable of rescuing the growth of a VP16-defective strain of HSV.

5. The requirement is still deemed proper and is therefore made FINAL.

6. Claims 1-12 and 27 in the scope of equine herpes virus gene 12 and HSV ICP4 are considered.

7. Applicants are reminded to amend the claims 3-4 and 10 within the scope of equine herpes virus gene 12 and HSV ICP4 for reflecting the examination on the merits.

8. Applicants are requested to cancel the claims 13-26 drawn to the non-elected groups.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-12 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1 and 8 are indefinite in that the metes and bounds of " a mutation" are not defined. The concept of mutation is defined by the change in a gene that leads to a sudden and stable alteration in the genome of a cell, virus or organism, which include the translocation, deletion, inversion, duplication and point mutation etc. (See word mutation on page 212, ILLUSTRATED DICTIINARY OF IMMUNOLOGY, edited by Cruse et al. 1994, CRC Press Inc.). The claim is interpreted in light of the specification, the specification, however, fails to define which mutation is intended. Is complete deletion of VP16 intended or substitution of certain amino acids of VP16 intended? If applicants wish to claim a particular mutation(s), the

claim should point out precisely what kind of mutation is intended in the claim. This affects the dependent claims 2-7, 9-12 and 27.

12. Claim 1 vague and indefinite in that the metes and bounds of " a homologue thereof" are not defined. Applicants are reminded that the concept of homology or sequence similarity can be calculated by a variety of different methods, whereby the calculated identity between two sequences will be quite different depending on the algorithm used for calculation. Furthermore, the calculation of "identity" is affected by variables such as the relative weight given to the sequence gaps versus mismatches, or whether conservative substitutions are weighted differently from non-conservative substitutions. Moreover, a homology can be variety of degree, applicants asserted in the response to the Office Action of Restriction/Election that only certain degree of homology is intended. However, this limitation does not define or appear in the claims. It is unclear which homology is intended. Is 90% homology of VP16 of HSV intended or 10% homology of VP16 of HSV intended. If Applicants wish to claim a particular peptide or polypeptide, please amend the claim to the particular peptide or polypeptide that is intended. This affects the dependent claim 2-12 and 27.

13. The claim 1 is also vague for recitation of a relative word "capable of", because the capability of a compound or composition to perform some function is merely a statement of a latent characteristic of said compound or composition and said language carries no patenable weight. Therefore, the claims are regarded as indefinite.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-12 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of propagating a mutated herpes simplex virus in 1814 (A mutated herpes virus made by inserting a 12-base-pairs of CGCGGATCCGCG, into the region of VP16 gene) or the said in 1816 HSV plus ICP4 mutation, in the cell line comprises

the full length of equine herpes virus EHV gene 12, does not reasonably provide enablement for having a method for propagating a mutant HSV with any or all kinds of VP16 gene mutation plus any one or more other additional endogeneous genes mutations in the cell line transfected with any or all homology of VP16 of HSV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

16. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors complied to the instant case have been analyzed as the following:

1) &2). State of the art/Unpredictability:

It is known in the art that EHV gene 12 is able to work in the same manner as that of VP16 of HSV to trans-activate both EHV-1 and HSV IE gene expression. However, not any or all fragment of the homologues of VP16 is able to efficiently trans-activate the HSV or EHV IE gene as evidenced by Elliott (J. Virol. 1994, Vol. 68, pp. 4890-4897). He teaches that the fragment of EHV gene 12 with truncation of 7 amino acids at its extreme C-terminus did not restore the activity to the HSV-1 protein. Therefore, it is unpredictable for using any or all homology fragment of the VP16 to trans-complementing the function of defective VP16.

3) & 4) Number of working examples and amount of guidance presented in the specification:

Applicants only teach that the full length of EHV gene 12 is able to trans-complement the function of HSV VP16 and CIP4.

The specification does not teach any or all homology of VP16 is able to trans-complement the defected function of VP16 in any or all kinds of mutated form.

The specification does not provide adequate guidance for selecting a homology of VP16 or deleting a homology of VP16 in such a way that any endogenous gene mutation can be trans-complemented by using any or all homology of VP16.

5) Scope of the claims:

The scope of the claims read broadly on a method for propagating any or all mutated HSV with a VP16 mutation plus any one or more other endogeneous gene mutations in any or all cell line transfcted to express any or all kinds of homologue of HSV VP16.

6) Nature of the invention and level of skill in the art:

The invention involves one of the most complex and high technology, which require a person with considerable knowledge and experiences for dealing the proper selection of mutation and homology to do the trans-complementation and rescuing defective virus in a large quantity of non-routing work with unpredicted success because the filed is unpredicted without adequate teaching and guidance.

Given the above analysis of the factors, which the courts have determined are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-2, 5-6, 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ace et al. (J. Virol. 1989, Vol. 63, pp. 2260-2269).

18. Ace et al. teach a method for growing a herpes simple virus mutant, in1814 comprising a functional mutation of VP16 gene. The method comprises the mutation of the HSV with insertion of 12-bases-paires of gene into the coding sequence of VP16 and growing the mutated HSV in the cell line that is transfected to express the VP16 homology of Mmw110. The in1814 viruses have been isolated and tested for their titration (See entire document). Therefore, the claimed invention is anticipated by the cited reference.

19. Claims 1-2, 5-6, 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriuchi et al. (J. Virol. 1993, Vol. 67, pp. 2739-2746).

20. Moriuchi et al. teach a method for growing a herpes simple virus mutant, in1814 (comprising a functional mutation of VP16 gene) in the cell line that is transfected to express the VP16 homology of Varicella-zoster virus VZV open reading frame 10 (ORF 10) protein, which is the homology of HSV-1 VP16. The viral complementation studies have been conducted by using the isolated in1814 viruses for testing their titration (See entire document). Therefore, the claimed invention is anticipated by the cited reference.

21. Claims 1-2, 5-6, 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Weinheimer et al. (J. Virol. 1992, Vol. 66, pp. 258-269)

22. Weinhermer et al. teach a method for growing a herpes simple virus mutant, in1814 (comprising a functional mutation of VP16 gene) in the cell line that is transfected to express the HSV-2 VP16, which is the homology of HSV-1 VP16. The viral complementation studies have been conducted by using the isolated in1814 viruses for testing their titration (See entire document). Therefore, the claimed invention is anticipated by the cited reference.

23. Claims 1-2, 5, 6, 7, 8, 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (J. Virol. 1994, Vol. 68, pp. 6347-6362).

24. Johnson et al. teach a method for rescue the VP16 and IE3 double mutated (14HΔ3) and/or UL42 triple mutated (14HΔ3vhsZ) HSV-1, wherein IE3 encodes the ICP4 gene. The rescue is done by superinfecting the cell line with a mutated HSV-1, which comprises the homology of the VP16 of HSV-1 (See entire document, especially the lines 7-44 on left col. of page 6350). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. Claims 1-12 and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over DeLuca (WO 98/15637A1) in view of Elliott et al. (Virology. 1995, Vol. 213, pp. 258-262).

The claims 1-12 and 27 are drawn to a method for propagating and composition comprising a mutated HSV virus, wherein the mutation is the VP16 gene or homology thereof or in addition with mutation of other gene, preferably, the ICP4 gene. The process comprises infecting a cell line with the mutated virus, wherein the cell line is transfected to express a functional herpes simplex virus (HSV) VP16 polypeptide or homologue thereof. Furthermore, the complementing homologue of HSV VP16 is capable of complementing the defective VP16 function but not undergo homologous recombination with the VP16 gene in the virus, preferably, the homology is the equine herpes virus gene 12.

DeLuca discloses a method of making a mutated HSV with ICP4 and VP16 mutations and a composition comprising the mutated HSV. DeLuca teach a method for complementing the defective ICP4, but he does not teach the method for complementing the VP16 with a homologue to the VP16 of HSV.

Elliott et al. teaches that the equine herpesvirus 1 gene 12 (EHV-1) is the homology of herpes simplex virus (HSV) VP16, which is a potent transactivator of HSV IE gene expression, which is capable of activating both the EHV-1 and HSV-1 IE promoters to the levels similar to that of VP16 (Fig 1 on page 259) . They concluded that despite the different between the two proteins, the mechanism of interaction of gene 12 protein of EHV-1 with its target is the analogous to that of VP16 of HSV (Abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the cited references to propagating a VP16 and ICP4 double mutated HSV in a cell line transfected to express EHV-1 gene 12 by combining the teachings from DeLuca and Elliott et al. with a highly expected success because the VP16 and ICP4 double mutated virus as disclosed by DeLuca is able to grow well in a cell line that is able to trans complement the defective function of ICP4, an additional trans complement of defective VP16 with HSV Vp16 homology, EHV-1 gene 12 would be able to provide a better condition for propagating this double mutated HSV-1. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
October 24, 2002

James C. Housel
JAMES HOUSEL 11/3/02
SUPERVISORY PATENT EXAMINER
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